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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/705,874	11/13/2003	Tian-Li Wang	001107.00391	8148

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EXAMINER	
MCGILLEM, LAURA L	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 11/16/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/705,874	WANG ET AL.	
	Examiner	Art Unit	
	Laura McGillem	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-85* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,15,18,20,24-38,40-42,52,56,58-61,71,75,76,81,84 and 85* is/are rejected.

7)☒ Claim(s) *6-14,16,17,19,21-23,39,43-51,53-55,57,62-70,72-74,77-80,82 and 83* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 November 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/4/04, 11/8/04*. 11/10/04
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Priority

It is noted that this application receives priority to Provisional Application 60/426,406, filed 11/15/2002.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3-4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 3 and 4 are vague and indefinite because they are drawn to the number of sequence tags of "the plurality of sequence tags" and it is not clear whether the claims refer to the plurality of sequence tags from the test cells or the plurality of sequence tags from the reference cells.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-2, 18, 20, 24 -28, 30-36, 59-60 and 84 are rejected under 35 U.S.C. 102(a) as being anticipated by Dunn et al (Genome Res. ePub on Nov. 4, 2002. Vol. 12. pp. 1756-1765, of record).

It is noted that the instant specification does not specifically define karyotyping, but does disclose that methods of karyotyping can determine changes in copy number of portions of the genome, such as gain or loss of whole chromosomes, or amplifications or deletions of genomic regions (paragraph 0015 of the instant specification).

Dunn et al teach characterization of genomes and examination of intraspecific genomic variation using positionally defined short sequence tags. Dunn et al teach that this method is useful for both prokaryotic and eukaryotic genomes (see page 1756, left column, 2nd paragraph, in particular), which reads on the genome of a test and a reference eukaryotic cell. Specifically, Dunn et al digest genomic DNA with one restriction enzyme, biotinylate both ends and further digest with a second restriction enzyme, such as NlaIII, to leave four-base ends (see page 1757, left column, first full paragraph and Figure 1, in particular), which reads on generating a population of sequence tags defined by two restriction endonuclease sites where the portions of the sequence tags are defined by a first endonuclease cleavage site at the first end of each portion and a second endonuclease cleavage site at the second end. Dunn et al teach that the sequence tags are numbered according to their order along the genomic DNA (see page 1759, left column, first full paragraph, for example), which reads on enumerating the sequence tags to determine the number of sequence tags in the

population from a window of contiguous genomic sequence tags. The number of sequence tags were compared to the number of sequence tags that were predicted for the genome of a reference cell based on the determination of the number of cleavage sites for the relevant restriction endonucleases, which revealed more numerous tags from highly repetitive regions of the chromosome and fewer sequence tags in more unique regions of the chromosome (see page 1758, right column, 1st full paragraph, and page 1759, right column, 1st full paragraph), which reads on comparing the number of a plurality of sequence tags in a population to the number of plurality of sequence tags for a reference cell. Dunn et al exemplify a sequence tag which was determined to be present four times in a genome, but was determined to be underrepresented in a test genome, and was later associated with a chromosomal region known for genetic variability. Dunn et al teach another example in which deletion of genomic DNA has occurred in the test cell genome, including the deletion of an entire locus (see page 1759, right column, 1st full paragraph, and page 1760, entire left column, in particular), which reads on determining a difference in the number of a plurality of a sequence tags present in the population from the number determined for a reference cell, which indicates a karyotypic difference between the test cell and the reference cell. Dunn et al teach that the above method is useful to compare genomic sequence tags between prokaryotic cells of the same species and is useful for both prokaryotic and eukaryotic genomes (see page 1756, left column, 2nd paragraph, in particular), which reads on the taught method where the test eukaryotic cell and the reference eukaryotic cell are of the same species.

Dunn et al teach that the generated sequence tags are ligated together to form concatamers which are cloned into plasmids to generate a library for sequencing analysis, which were enumerated for a total of 5432 sequence tags from the sequenced concatamers (see page 1759, left column, 2nd and 3rd paragraph, for example), which reads on enumerating by determining the sequence of said sequence tags and recording the number of occurrences of individual sequence tags.

Dunn et al also teach dimers comprising two sequence tags described above which have been generated by cleavage with two endonucleases, first NotI or BamHi and second NlaIII to generate specific 4-bp ends, biotinylated, digested with MmeI to generate a defined length of ~21 bp and ligated together on the end opposite from that digested with NlaIII, the second endonuclease and concatamerized (see page 1757, left column, paragraphs 2 and 3, and Figure 1, for example) which reads on a dimer comprising two distinct sequence tags defined by two endonuclease cleavage sites, wherein each tag consists of a fixed number (~21 bp) of nucleotides of the genome portions extending from one of the endonuclease cleavage sites, and wherein the two tags are joined end-to-end at the end distal to the second endonuclease recognition site.

Dunn et al exemplify that the ~4 Mb prokaryotic cell genome was digested with endonucleases and processed as described above to form multiple concatamers of ligated dimers, or libraries, which are several hundred base pairs to <1kb in length, which were then cloned into vectors for sequencing (see page 1759, left column, 1st paragraph) which reads on a plurality of windows of sequence tags or pieces of the

genome. The data presented by Dunn et al was determined from one such library, which reads on the methods of karyotyping from a plurality of sequence tags in a window of contiguous sequence tags, but Dunn et al also disclose that their method provides a means for genome-wide fingerprinting of chromosomes (see page 1763, left column, 3rd paragraph, in particular), which reads on a method of determining a karyotypic difference comprising identifying pieces of the genome of the test cell by determining the nucleotide sequence of said pieces and enumerating the pieces of a plurality of windows of a fixed size (i.e. <1kb in length) and comparing the number of pieces counted within each of the plurality of windows for the test cell to pieces for a reference cell, wherein the test cell and reference cell are of the same species. Dunn et al teach that sequence tags were sequenced and matched to the reference genome and 97 % of the tags exactly matched at genome sites (see page 1759, left column, 3rd paragraph), which reads on matching piece of the genome to precise locations on the genome.

Claims 1-2, 15 and 59-60 are rejected under 35 U.S.C. 102(a) as being anticipated by Li et al (International Publication No. WO 02/002805, 1/10/2002).

Li et al teach a method for determining differences between DNA samples from two sources, including the same source but under different conditions (see page 1, lines 28-31, for example). Li et al teach that restriction enzymes are used to fractionate DNA into subpools of various sizes which are then ligated together and amplified (see page 5, lines 5-15, and page 15, lines 4-25 for example), which reads on generating a

populations of sequence tags, wherein the plurality of sequence tags are within windows of sequence tags. Li et al teach that the DNA used in this method can be genomic DNA derived from a plant or an animal (see page 7, lines 19-20, for example), which reads on using a test eukaryotic cell. Li et al also teach that the pattern of DNA fragments from the test cell is determined and compared to the DNA fragment pattern of normal cells. Li et al teach that a change in the pattern of DNA fragments is determined by quantitating a change in the number and size of the DNA fragments between the diseased cell, such as a cancer cell, and the normal cell chromosomal arrangement (see page 9, lines 1-21, for example), which reads on enumerating sequence tags in a population and comparing the number of the sequence tags in the population to the sequence tags determined of the genome of a reference cell, wherein a difference in the number of the sequence tags from the number determined for a reference cell indicates a karyotypic difference.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 5, 15, 29, 37-38, 40-42, 52, 56, 58, 61, 71, 75-76, 81 and 85 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 6,498,013 (Velculescu et al, of record) filed 7/27/2001, in view of Dunn et al (Nov. 4, 2002, of record).

Applicants claim a method of karyotyping a genome of a test eukaryotic cell by generating a population of sequence tags defined by restriction endonuclease sites from the genome of the test eukaryotic cell, enumerating the sequence tags and comparing the number of sequence tags to the number of sequence tags calculated to be present in the human genome to determine karyotypic abnormality. Applicants claim a method of karyotyping a genome by enumerating pieces of a genome of a test cell and enumerating the pieces within a plurality of windows to determine karyotypic abnormality. Applicants claim a dimer comprising two sequence tags from a eukaryotic cell from endonuclease recognition sites consisting of a fixed number of nucleotides extending from the restriction endonuclease recognition sites, wherein the eukaryotic cell is a human cell.

It should be noted that the Applicants do not specifically define karyotypic abnormality in the specification and therefore karyotypic abnormality will be interpreted as claimed to mean a difference in the number of sequence tags by insertion or deletion between a test eukaryotic cell and the human genome.

Velculescu et al teach a method of serial analysis of gene expression (longSAGE) for human genomic data comprising analysis of long sequence tags defined by endonuclease recognition sites that were generated from human mRNA for the purpose of quantitative comparison of expressed transcripts in a variety of normal and disease states (see column 3, lines 1-5, for example). Velculescu et al generate dimerized tags, or ditags, comprising two sequence tags from a eukaryotic cell from endonuclease recognition sites consisting of 17-21 nucleotides extending from the

restriction endonuclease recognition sites which are concatamerized and cloned for sequencing (see column 2, lines 40-67, for example). Velculescu et al teach that some clones used have at least 10 sequence tags of a range of 10-50 tags (see column 15, lines 17-26, for example), which reads on a window of sequence tags comprising 10-500 contiguous tags, and 50 to 1000 contiguous sequence tags. Velculescu et al teach that the sequence tag data generated from the test cell is then compared to known human genome data (see column 12, lines 5-15 and lines 31-35) and matched to the corresponding genomic database (see column 12, lines 59-67 and column 13, lines 1-3, for example). Velculescu et al teach that the method can be used for comparison of gene expression between pathological and normal tissue, which is useful for identifying diagnostically, prognostically and therapeutically important genes (see column 22, lines 31-40, for example) which reads on determining a difference in sequence tags in a test cell compared to a normal cell to discover an abnormality. Velculescu et al exemplify sequence tags from colon cancer cells (see column 7, lines 32-35, for example), which reads on a test cell being a cancer cell. Velculescu et al do not teach production of sequence tags from genomic DNA.

As described in the above 35 U.S.C. 102 (a) rejection, Dunn et al teach a method of karyotyping a genome of a test eukaryotic or prokaryotic cell by generating a library of sequence tags defined by endonuclease recognition sites including NlaIII, concatamerizing the sequence tags for sequencing and numbering (see page 1757, left column, in particular). Dunn et al also teach that the number of sequence tags generated from the test cell is compared to the number of sequence tags calculated to

be present in a reference cell (see page 1759, left column, 2nd and 3rd paragraph and right column, 1st full paragraph). Dunn et al teach that tags were sequenced and matched to the reference genome and that 97% of the tags exactly matched at genome sites (see page 1759, left column, 3rd paragraph), which reads on matching piece of the genome to precise locations on the genome. In addition, Dunn et al teach that comparison of the number of sequence tags between the test cell and the reference cell revealed that some sequence tags that were predicted to be present in the reference cell were not present in the test cell, and were deletions or rearrangements of the test cell genome (see page 1760, left column, for example), which reads on a difference in the number of sequence tags present in the population of sequence tag between a test cell and a reference cell indicating a karyotypic abnormality.

As described above, Dunn et al disclose an embodiment of their method which provides a means for genome-wide fingerprinting of chromosomes (see page 1763, left column, 3rd paragraph, in particular), which reads on a method of determining a karyotypic difference comprising identifying pieces of the genome of the test cell by determining the nucleotide sequence of said pieces and enumerating the pieces of a plurality of windows of a fixed size (i.e. <1kb in length) and comparing the number of pieces counted within each of the plurality of windows for the test cell to pieces for a reference cell, wherein the test cell and reference cell are of the same species.

It would have been obvious to one of ordinary skill in the art to modify the method of Velculescu et al to examine genomic DNA from eukaryotic human test cells to compare to the number of sequence tags that are predicted to be present in the

human genome, because Dunn et al teach the use of eukaryotic cells and that the longSAGE method can be easily modified to obtain genomic sequence tags by starting with genomic DNA fragments rather than poly(A)$^+$ derived cDNA (see page 1763, left column, 1st full paragraph). Velculescu et al teach that RNA transcripts expression can be examined using a very similar method to that of Dunn et al comprising generating sequence tags with endonuclease activity and creating dimers of the sequence tags for further concatamerization, sequencing and analysis. The motivation to do so is the expected benefit of the ease and speed of the method of Dunn et al to determine karyotypic difference between genomic sequence tags of a test eukaryotic cell and the human genome. There is reasonable expectation of success to use human cells in the method of Dunn et al it has worked previously in the cited techniques. Given the teachings of the prior art and the level of skill of the ordinary skilled artisan at the time the invention was made, it must be considered that said ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Conclusion

Claims 6-14, 16-17, 19, 21-23, 39, 43-51, 53-55, 57, 62-70, 72-74, 77-80 and 82-83 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura McGillem whose telephone number is (571) 272-8783. The examiner can normally be reached on M-F 8:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Laura McGillem, PhD
11/10/05

DAVID GUZO
PRIMARY EXAMINER